REMARKS

Claims 1-37 remain pending in the application. In an effort to expedite prosecution of this application and in no way conceding to any of the rejections of record, claims 1, 29, 36 and 37 have been amended as follows.

Claims 1 and 29 have been amended to specify that the claimed compositions do not include a combination of auranofin and betamethazone dipropionate. Claims 36 and 37 have been amended to be in proper dependent form.

Attached hereto is a marked up version of the changes made to the claims by the instant Amendment. The attached page is captioned **"Version With Markings to Show Changes Made."** For the Examiner's convenience, a clean copy of all of the claims that will be pending upon entry of the present Amendment is also attached hereto as Appendix A.

No new matter has been added. Applicants reiterate that any amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite prosecution of this application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Objection to Claims 36 and 37 Under 37 CFR § 1.75(c)

The Examiner objects to claims 36 and 37 under 37 CFR § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim.

In response, Applicants have amended claims 36 and 37 to be in proper dependent form, thereby rendering the objection moot. Accordingly, Applicants request withdrawal of the objection to claims 36 and 37 under 37 CFR § 1.75(c).

Rejection of Claims 1-5, 7-8, 11-15, 18, 21-22, 27 and 29-37 Under 35 U.S.C. § 102(b)

The Examiner rejects claims 1-5, 7-8, 11 -15,18, 21, 22, 27 and 29-37 under 35 U.S.C. §102(b) as being anticipated by Papandrea (US Pat. No. 5,527,779). Specifically, the Examiner is of the opinion that:

> Papandrea teach a composition comprising a gold compound and a corticosteroid for the treatment of local or systemic inflammatory conditions. . .. The reference teaches (1) gold compounds such as aurothiomalate, aurothioglucose and auranofin; (2) corticosteroid such as betamethasone dipropionate; and (3) the synergistic effect between auranofin and corticosteroids as well as the concomitant or sequential use of the compounds.

The Examiner concludes that "[t]he composition and method of use taught by the reference are encompassed by the instant claims." Applicants respectfully traverse this rejection.

From the outset, as amended, the pending claims have been amended to specifically exclude compositions (and the use of such compostions) comprising a combination of auranofin and betamethazone dipropionate. In view of the fact that betamethazone dipropionate is the only corticosteroid in combination with a gold compound taught by Papandrea, the newly amended claims are clearly not anticipated by this reference.

Moreover, as amended, the pending method claims are drawn to the treatment of an immune-mediated disorder having an inflammatory component and/or a cellular hyperproliferation component by administering a gold compound and at least one corticosteroid which is selected to interact with the gold compound to exhibit preferential synergistic action towards one of the components of said disorder or to exhibit equal action towards each component of said disorder. Similarly, as amended, the pending composition claims are drawn to pharmaceutical compositions comprising a gold compound and one or more corticosteroids, wherein the corticosteroid is selected to interact with the gold compound to exhibit a preferential synergistic action towards an inflammatory component and/or a cellular hyperproliferation component of an immune-mediated disorder.

Thus, the pending claims are collectively drawn to therapeutic methods and pharmaceutical compositions containing one or more corticosteroids which are selected to interact with a gold compound such that the corticosteroid provides a particular therapeutic effect, namely a preferential synergistic action against an inflammatory and/or a proliferative disorder, or equal action towards each of these disorder components.

In contrast, Papandrea does not teach or suggest the selection of any corticosteroid based on such effects (e.g., its action towards a component of an immune-mediated disorder), much less corticosteroids other than betamethazone dipropionate, as claimed by Applicants. Indeed, Papandrea fails to disclose or compare the anti-inflammatory vs. anti-proliferative effects of different corticosteroids with a gold compound, **or even that such differential effects exist**.

Instead, Papandrea merely exemplifies one combination of a gold compound and a corticosteroid (namely auranofin in combination with betamethazone dipropionate) and makes no reference to the differential synergy of other corticosteroids with auranofin or any other gold-containing compounds. Thus, Papandrea does not teach the selection of a particular corticosteroid to interact with a gold compound on any basis, much less the selection of a corticosteroid based on the differential synergistic interaction of the selected corticosteroid with the gold containing compound, as claimed by Applicants.

Accordingly, Applicants request reconsideration and withdrawal of the rejection of claims 1-5, 7-8, 11 -15,18, 21, 22, 27 and 29-37 under 35 U.S.C. §102(b) as being anticipated by Papandrea.

Rejection of Claims 1-5, 7-8, 11-15, 18, 21-22, 27 and 29-37 Under 35 U.S.C. § 102(e)

The Examiner also rejects claims 1 -5, 7-8, 11 -15,18, 21-22, 27 and 29-37 under 35 U.S.C. §102(e) as being anticipated by Papandrea (US Pat. No. 5,527,779). Specifically, the Examiner is of the opinion that:

> Papandrea teach a composition comprising a gold compound and a corticosteroid for the treatment of local or systemic inflammatory conditions. . .. The reference teaches (1) gold compounds such as aurothiomalate, aurothioglucose and auranofin; (2) corticosteroid such as betamethasone dipropionate; and (3) the synergistic effect between auranofin and corticosteroids as well as the concomitant or sequential use of the compounds.

The Examiner concludes that "[t]he composition and method of use taught by the reference are encompassed by the instant claims." Applicants respectfully traverse and request reconsideration.

As discussed above in the previous subsection (i.e., Applicants' response to the same rejection under 102(b)), the pending claims as amended herein are novel over the teachings of Papandrea. In brief, Papandrea does not teach suggest the selection of any corticosteroid based on such effects (e.g., its action towards a component of an immune-mediated disorder), much less corticosteroids other than betamethazone. Thus, the reference does not anticipate the presently claimed invention, which is drawn to methods and pharmaceutical compositions containing one or more corticosteroids which are selected to interact with a gold compound such that the corticosteroid provides a particular therapeutic effect, namely a preferential synergistic action against an inflammatory and/or a proliferative disorder, or equal action towards each of these disorder components.

Accordingly, Applicants request reconsideration and withdrawal of the rejection of claims 1 -5, 7-8, 11 -15,18, 21-22, 27 and 29-37 under 35 U.S.C. §102(e) as being anticipated by Papandrea (US Pat. No. 5,527,779).

Rejection of Claims 1-37 Under 35 U.S.C. § 103(a)

The Examiner rejects claims 1-37 under 35 U.S.C. §103(a) as being unpatentable over Papandrea (AU-34351/89 or US 5,527,779). The Examiner acknowledges that claims 15, 16-17 and 35-36 "differ from the references by reciting additional corticosteroids not exemplified by the cited prior art." The Examiner also acknowledges that claims 6, 10, 16-17, 19-20, 23-25 and 28 differ from the references by reciting the administering of at least two corticosteroids, by reciting the treatment of rheumatoid arthritis and by reciting various routes of administration. However, the Examiner is of the opinion that "the combination of one or two corticosteroids with a gold compound for the treatment of an immune-mediated disorders, such as rheumatoid arthritis, dermatitis and psoriasis, would have been obvious to one having ordinary skill in the art at the time of the invention and the administration of the composition by the recited routes of administration is within the level of skill of the ordinary artisan and, thus, is prima facie obvious." Applicants respectfully traverse this rejection and request reconsideration.

Like Papandrea (US 5,527,779), Papandrea (AU-34351/89) fails to teach or suggest the selection of any corticosteroid based on its synergistic or equal action towards one or more components of an immune-mediated disorder when combined with a gold compound, as claimed by Applicant. Nor do either of these references even suggest that corticosteroids have such differential synergistic interactions when combined with gold compounds. Therefore, these references would not have made the instantly claimed invention, based on the discovery of such differential interaction among corticosteroids with gold compounds, in any way obvious.

Indeed, given that the cited Papandrea publications provide only one example of a gold compound and a corticosteroid (*i.e.,* the combination of auranofin and betamethazone dipropionate), they would not have provided any motivation for one of skill in the art to have tried to have made or practiced the presently claimed invention which requires selection of specific corticosteroids based on their differential synergistic interaction with a gold compound. Moreover, based on the fact that neither Papandrea reference provides any guidance whatsoever on how such selections are made, these references also fail to provide any reasonable expectation of success in achieving the instantly claimed invention.

The Examiner also cites DeLong et al. (US 3,937,822), Weyburn-Mason (US 4,119,723) and Wolf (US 4,267,192) as exemplifying the use of corticosteroids and gold compounds to treat rheumatoid arthritis, dermatitis and psoriasis. However, like the Papandrea references, these references fail to teach or suggest the differential synergistic interaction between gold compounds and corticosteroids.

DeLong et al. teaches the administration of pyrazofurin to treat psoriasis. Pyrazofurin is neither a gold-containing compound nor a corticosteroid and therefore has no relevance to the subject matter of the present invention. Even if the Examiner is referring to the information provided in the Background section of DeLong et al., wherein at column 1, lines 20-30, it is stated that agents "commonly used in treating psoriasis include ... topical corticosteroids such as fluocinolone acetonide, fluorandrenolide and triamcinolone acetonide," this statement does not teach or suggest the differential synergistic interaction between gold compounds and corticosteroids. Thus, DeLong et

al., neither alone nor in combination with the Papandrea publications, teaches the subject matter claimed in the present application, namely the discovery of differential synergistic interaction between corticosteroids and gold compounds.

Wyburn-Mason teaches the administration of tinidazole and related compounds to treat rheumatoid arthritis and related collagen and auto-immune diseases. Applicants once again emphasize that tinidazole is neither a gold-containing compound nor a corticosteroid and, therefore, that Wyburn-Mason has no relevance to the subject matter claimed in the present application. Wyburn-Mason states in the Background section at column 1, lines 40 to 42 that "chemical compounds which have been commonly used in treating rheumatoid arthritis are corticosteroids, gold salts, antimalarial drugs, immunosuppressive agents ...." However, this statement does not teach or suggest the differential synergistic interaction between gold compounds and corticosteroids, as discovered and claimed by Applicants. Thus, Wyburn-Mason, neither alone nor in combination with the Papandrea publications, renders obvious the subject matter claimed by Applicants, namely the discovery of differential synergistic interactions between corticosteroids and gold compounds.

Similarly, Wolf teaches the administration of dibenzocycloheptenylidenes to treat inflammation in mammals. Applicants again note that dibenzocycloheptenylidene is neither a gold-containing compound nor a corticosteroid and therefore has no relevance to the subject matter claimed in the present applicaiton. In the Background section, at column 1, lines 7 to 14 Wolf states that "[i]n the treatment of chronic inflammatory conditions, both steroidal and nonsteroidal drugs have been extensively used." However, this statement certainly does not teach or suggest the differential synergistic interaction between gold compounds and corticosteroids, as claimed by Applicants.

Moreover, since none of the methods taught by DeLong et al., Wyburn-Mason and Wolf for treating psoriasis and rheumatoid arthritis include the use of either a corticosteroid or a gold compound, much less a selected combination of these two compounds as claimed by Applicants, these references certainly would not have rendered the instantly claimed invention obvious. Indeed, the fact that these references teach

effective alternative methods and compounds for treating these diseases would have led one of ordinary skill in the art away from the instantly claimed invention.

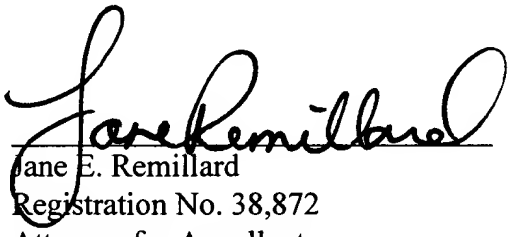
Accordingly, for at least the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-37 under 35 U.S.C. §103(a) as being unpatentable over the Papandrea publications.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



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Dated: **February 26, 2001**

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 1, 29, 36 and 37 have been amended as follows:

1. (Amended) A method of treating an immune-mediated disorder having an inflammatory component and/or a cellular hyperproliferation component, comprising the step of administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit preferential synergistic action towards one of the components of said disorder or to exhibit equal action towards each component of said disorder, provided that said method does not include the administration of a combination of auranofin and betamethazone dipropionate.

29. (Amended) A pharmaceutical composition comprising a gold compound and one or more corticosteroids, the corticosteroid being selected to interact with the gold compound to exhibit a preferential synergistic action towards an inflammatory component and/or a cellular hyperproliferation component of an immune-mediated disorder, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent, provided that said composition does not include auranofin and betamethazone dipropionate.

36. (Amended) A pharmaceutical composition ~~method~~ according to claim 35 wherein the corticosteroid is selected from the group consisting of hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

37. (Amended) A pharmaceutical composition ~~method~~ according to claim 29, wherein the gold compound is auranofin.

APPENDIX A

1. A method of treating an immune-mediated disorder having an inflammatory component and/or a cellular hyperproliferation component, comprising the step of administering to a patient requiring such treatment a gold compound and at least one corticosteroid, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit preferential synergistic action towards one of the components of said disorder or to exhibit equal action towards each component of said disorder, and provided that said method does not include the administration of a combination of auranofin and betamethazone dipropionate.

2. A method of treating an immune-mediated disorder according to claim 1, wherein the disorder has an inflammatory component and a cellular hyperproliferation component.

3. A method of treating an immune-mediated disorder according to claim 1, wherein the gold compound and the at least one corticosteroid are administered simultaneously.

4. A method of treating an immune-mediated disorder according to claim 1, wherein the gold compound and the at least one corticosteroid are administered sequentially.

5. A method of treating an immune-mediated disorder according to claim 4, wherein the at least one corticosteroid is administered after the gold compound.

6. A method of treating an immune-mediated disorder according to claim 1 comprising the step of administering at least two corticosteroids, at least one of which is selected to interact with the gold compound to exhibit preferential synergistic action towards the inflammatory component, and at least another is selected to interact with the

gold compound to exhibit preferential synergistic action towards the cellular hyperproliferation component of said disorder.

7. A method according to claim 1, wherein the disorder is an immune-mediated dermatological disorder.

8. A method according to claim 7, wherein the disorder is psoriasis.

9. A method according to claim 7, wherein the disorder is dermatitis.

10. A method according to claim 1, wherein the disorder is rheumatoid arthritis.

11. A method according to claim 1, wherein the gold compound is lipid soluble.

12. A method according to claim 1, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit synergistic activity towards cellular hyperproliferation in preference to inflammation.

13. A method according to claim 12, wherein the at least one corticosteroid is selected from the group consisting of betamethasone dipropionate, fluocinolone acetonide and hydrocortisone.

14. A method according to claim 1, wherein the at least one corticosteroid is selected to interact with the gold compound to exhibit synergistic activity towards inflammation in preference to cellular hyperproliferation.

15. A method according to claim 14, wherein the at least one corticosteroid is selected from the group consisting of betamethasone dipropionate, fluocinolone acetonide and mometasone furoate.

16. A method according to claim 10, wherein the corticosteroid is selected from the group consisting of hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-privalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate and fluocinolone acetonide.

17. A method according to claim 16, wherein the corticosteroid is selected from the group consisting of hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

18. A method according to claim 1, wherein the gold compound is auranofin.

19. A method according to claim 1, wherein the gold compound is administered systemically.

20. A method according to claim1, wherein the gold compound is administered orally.

21. A method according to claim 1, wherein the gold compound is administered locally.

22. A method according to claim 1, wherein the gold compound is administered topically.

23. A method according to claim 1, wherein the gold compound is administered by intra-articular injection.

24. A method according to claim 1, wherein the at least one corticosteroid is administered systemically.

25. A method according to claim 1, wherein the at least one corticosteroid is administered orally.

26. A method according to claim 1, wherein the at least one corticosteroid is administered locally.

27. A method according to claim 1, wherein the at least one corticosteroid is administered topically.

28. A method according to claim 1, wherein the at least one corticosteroid is administered by intra-articular injection.

29. A pharmaceutical composition comprising a gold compound and one or more corticosteroids, the corticosteroid being selected to interact with the gold compound to exhibit a preferential synergistic action towards an inflammatory component and/or a cellular hyperproliferation component of an immune-mediated disorder, in combination with a pharmaceutically acceptable carrier, excipient, adjuvant or solvent, provided that said composition does not include auranofin and betamethazone dipropionate.

30. A pharmaceutical composition according to claim 29, wherein the composition is formulated for systemic administration.

31. A pharmaceutical composition according to claim 29, wherein the composition is formulated for oral administration.

32. A pharmaceutical composition according to claim 29, wherein the composition is formulated for local administration.

33. A pharmaceutical composition according to claim 29, wherein the composition is formulated for topical administration.

34. A pharmaceutical composition according to claim 29, wherein the composition is formulated for administration by intra-articular injection.

35. A pharmaceutical composition according to claim 29, wherein the corticosteroid is selected from the group consisting of hydrocortisone acetate, hydrocortisone, betamethasone, betamethasone dipropionate, dexamethasone, fluocortolone 21-privalate, triamcinolone acetonide, betamethasone valerate, alclometasone dipropionate, halcinonide, mometasone furoate and fluocinolone acetonide.

36. A pharmaceutical composition according to claim 35 wherein the corticosteroid is selected from the group consisting of hydrocortisone, betamethasone dipropionate, mometasone furoate and fluocinolone acetonide.

37. A pharmaceutical composition according to claim 29, wherein the gold compound is auranofin.